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PATENT SPECIFICATION

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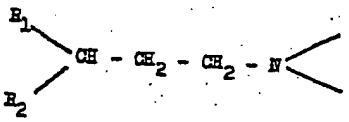
COMPLETE SPECIFICATION

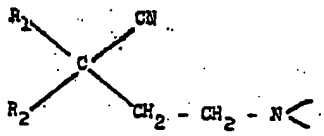
Basically Substituted Propane Compounds and the Manufacture thereof

We, MICHAEL EHLENBACH and ADOLF SIEGLITZ, both German citizens, and of Georg Voigtstrasse 12, Frankfurt (Main), Germany, and Oranienstrasse, Bad Soden (Taunus), Germany, respectively, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention consists in a process for the manufacture of the basic compounds of the general formula



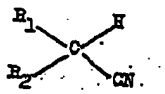
in which R_1 represents an unsubstituted or substituted phenyl group, R_2 represents a heterocyclic radical and —N< represents a tertiary-bound nitrogen atom, wherein a nitrile of the general formula



in which R_1, R_2 and —N< have the meanings given above, is treated with an alcoholic solution of an alkali hydroxide to replace the nitrile group by hydrogen.

As the alkali hydroxide there may be used potassium hydroxide.

The nitriles used as starting materials in the present process may be obtained by reacting a nitrile of the general formula

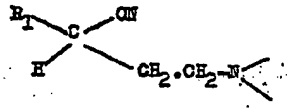


in which R_1 and R_2 have the meanings given above, with a basically substituted alkyl halide of the general formula

$$Hal—CH_2—CH_2—N<$$

in which N< has the meaning given above, in the presence of sodamide or another agent capable of eliminating hydrogen halide. Halides of this kind are, for instance, N-β-chlorethyl-dimethylamine, N-β-chlorethyl-diethylamine, 1-chloro-2-dimethylamino-propane, N-β-chlorethyl-piperidine, N-β-chlorethyl-pyrrolidine and N-β-chlorethyl-morpholine.

Alternatively the nitriles may be obtained by reacting a nitrile of the general formula

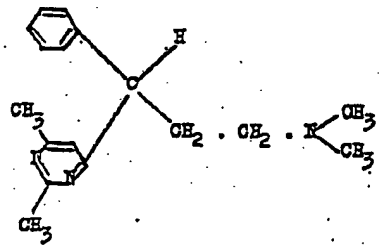


in which R_1 and N< have the meanings given above, with a halogen-substituted heterocyclic compound in the presence of sodamide or another agent capable of eliminating hydrogen halide. As halogen-substituted heterocyclic compounds there may be used, for example 2-chloropyridine, 2-chlorothiazole, 2:6-dimethyl-4-chloropyrimidine, 2-chlorobenzthiazole or 4-chloroquinoline.

The products of the present invention are more or less viscous oils, which can be converted into salts which dissolve

[Price 2/8]

well in water, and among which salts the phosphates have been found to be especially useful. The products exhibit excellent antispasmodic properties which are especially pronounced in the case of histamine spasms. There come into consideration more especially 1-phenyl-1-thiazole-(2')-3-dimethyl - aminopropane and 1 - phenyl - 1 - [2':6' - dimethyl-pyrimidyl-(4')]-3-dimethylamino-propane of the formula



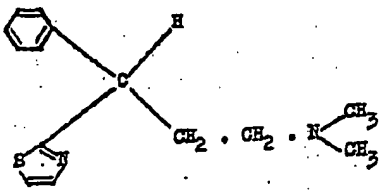
which boils at 122—126° C. under a pressure of 0.1 mm.

The following Examples illustrate the invention, the parts being by weight:—

EXAMPLE 1.

94 parts of α-phenyl-γ-dimethylamino-butyric acid nitrile are heated for 1 hour at 80° C. together with 200 parts of toluene and 22 parts of sodamide. After cooling, 60 parts of 2-chlorothiazole are added, and the product of the reaction is heated for 2 hours at 110° C. After decomposing the reaction product with water and separating the organic solution, there is obtained by fractional distillation, after a small quantity of first runnings, α-phenyl-α-thiazolyl - (2) - γ - dimethyl-amino-butyric acid nitrile boiling at 150—153° C. under a pressure of 0.25 mm. in a very good yield.

By heating the product for 2 hours with an excess of an alcoholic solution of potassium hydroxide, 1 - phenyl - 1-thiazolyl-(2')-3-dimethylamino-propane of the formula

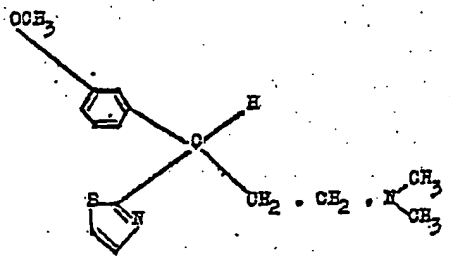


boiling at 136—138° C. under a pressure of 0.6 mm. is obtained in a very good yield. The phosphate containing two molecular proportions of water of crystallisation melts at 78—80° C.

EXAMPLE 2.

65.4 parts of α-(3-methoxyphenyl)-γ-dimethyl-amino-butyric acid nitrile (prepared from 3-methoxy benzyl cyanide, β - chlorethyl - dimethylamine and sodamide), 150 parts of toluene and 12.5 parts of sodamide are reacted with 36 parts of 2-chlorothiazole, and the product is heated for 1½ hours at about 110° C. The product is decomposed with water and subjected to a fractional distillation. α - (3 - Methoxy phenyl) - α - thiazolyl-(2)-γ-dimethylammino-butyric acid nitrile distils in good yield at a temperature of 155—160° C. under a pressure of 0.15 mm. in the form of a highly viscous yellow oil.

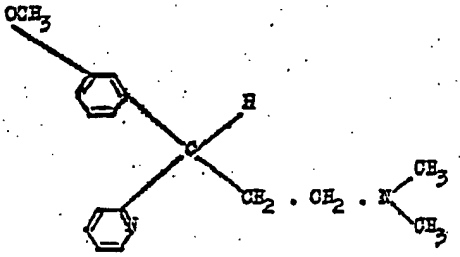
The nitrile group is then eliminated by treatment with an alcoholic solution of potassium hydroxide as described in Example 1 and there is obtained 1-(3'-methoxyphenyl) - 1 - thiazolyl - (2') - 3-dimethylaminopropane of the formula



boiling at 150—154° C. under a pressure of 0.5 mm.

EXAMPLE 3.

32.5 parts of α-(3-methoxyphenyl-γ-dimethylamino-butyric acid nitrile, 100 parts of toluene and 6 parts of sodamide are reacted with 17 parts of 2-chloropyridine. By fractional distillation of the reaction product α-(3-methoxyphenyl)-α-pyridyl-(2)-γ-dimethylamino-butyric acid nitrile is obtained in a good yield, in addition to unchanged starting material. The product so obtained is a viscous reddish oil boiling at 168—170° C. under a pressure of 0.3 mm., from which, by eliminating the nitrile group in the manner described in Example 1, there is readily obtained the corresponding propane of the formula

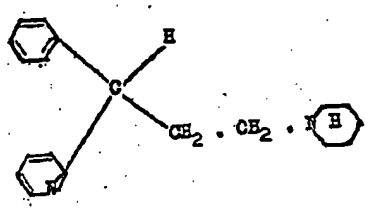


which boils at 155—160° C. under a pressure of 0.5 mm.

EXAMPLE 4.

13 parts of sodamide are introduced at 25—35° C. into a solution of 58.3 parts of phenyl - pyridyl-(2)-acetonitrile in 200 parts of benzene. The mixture is heated for a short time at 60—70° C. It is then cooled, and 48.5 parts of piperidino-ethyl chloride (boiling at 68—70° C. under a pressure of 12 mm.) are introduced dropwise. On heating to 50—60° C. the reaction sets in. Finally the reaction product is heated for 1 hour to 80° C., decomposed with water, and the benzene solution is separated. After a small amount of first runnings has distilled, α-phenyl-α-pyridyl-(2) - γ - (N-piperidino)-butyric acid nitrile distils at 185—190° C. under a pressure of 0.4 mm. in a yield of 90—95 per cent. in the form of a red viscous oil.

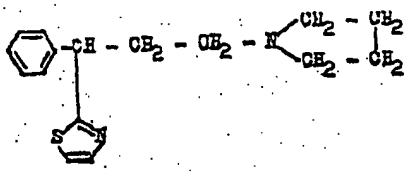
By treatment with an alcoholic solution of alkali 1-phenyl-1-pyridyl-(2')-3-piperidino-propane of the formula



is obtained in a very good yield in the form of a slightly coloured viscous oil boiling at 160—164° C. under a pressure of 0.25 mm.

EXAMPLE 5.

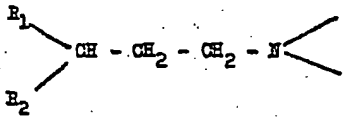
48 parts of α-phenyl-γ-N-pyrrolidino-butyric acid nitrile, boiling under a pressure of 0.1—0.2 mm. at 130—134° C., are heated for 30 minutes at 70—80° C. with 9.3 parts of sodamide in 200 parts of toluene, and, after cooling, gradually mixed with 27 parts of 2-chloro-thiazole at a temperature of 25—40° C. The mixture is heated for one hour at 90—95° C., mixed with 150 cc. of water, the toluene solution is separated and fractionally distilled. In addition to unchanged starting materials, α-phenyl-α-thiazolyl-(2)-γ-N-pyrrolidino-butyric acid nitrile is obtained as a viscous yellow oil boiling at 165—168° C. under a pressure of 0.15 mm. and melting at 83—85° C. 25 parts of this nitrile are boiled under reflux on the steam bath for 4 hours with 10 parts of caustic soda, 100 parts of ethyl alcohol and 10 parts of water. By working up in the usual manner 1-phenyl-1-thiazolyl-(2') - 3 - N - pyrrolidino - propane of the formula



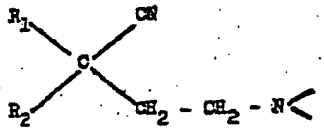
is obtained boiling at 136—139° C. under a pressure of 0.1 mm.

What we claim is:—

1. A process for the manufacture of the basic compounds of the general formula



in which R_1 represents an unsubstituted or substituted phenyl group, R_2 represents a heterocyclic radical and —N< represents a tertiary-bound nitrogen atom, wherein a nitrile of the general formula

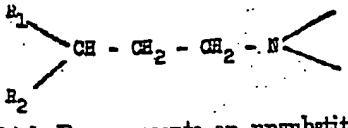


in which R_1, R_2 and —N< have the meanings given above, is treated with an alcoholic solution of an alkali hydroxide to replace the nitrile group by hydrogen.

2. A process as claimed in claim 1, wherein the alkali hydroxide is potassium hydroxide.

3. A process for the manufacture of the basic compound of any one of the Examples herein conducted substantially as described in that Example.

4. Basic compounds of the general formula

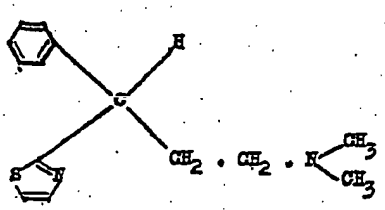


in which R_1 represents an unsubstituted or substituted phenyl group, R_2 represents a heterocyclic radical and —N< represents a tertiary-bound nitrogen atom, when obtained by the process claimed in any one of claims 1—3.

5. Basic compounds as claimed in claim 4, wherein N< represents a dialkylamino group.

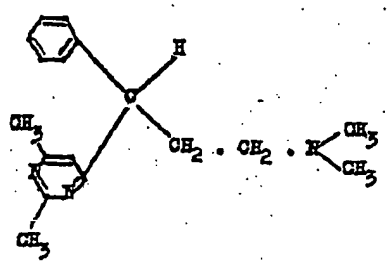
6. Basic compounds as claimed in claim 4, wherein N< represents a heterocyclic amino group.

7. 1 - Phenyl - 1 - thiazolyl-(2')-3-dimethylaminopropane of the formula



boiling at 136—138° C. under a pressure of 0.6 mm., when obtained by the process claimed in any one of claims 1—3.

8. 1 - Phenyl - 1 - [2':6' - dimethylpyrimidyl-(4')] - 3 - dimethylaminopropane of the formula



boiling at 122—126° C. under a pressure of 0.1 mm., when obtained by the process claimed in claim 1 or 2.

9. Any one of the basic compounds specified as end products of Examples 2—5 when obtained by the method substantially as described in that Example.

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